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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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KNOBBE, MARTENS, OLSON & BEAR, LLP
2040 MAIN STREET
IRVINE, CA 92614

EXAMINER	
KEMMERER, ELIZABETH	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 04/21/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/941,992	ASHKENAZI ET AL.	
	Examiner	Art Unit	
	Elizabeth C. Kemmerer, Ph.D.	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 March 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *124-126 and 129-131* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *124-126 and 129-131* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/30/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments, And/Or Claims

The Decision on Petition (mailed 30 January 2006) is noted. Accordingly, Applicant's request for reconsideration of the finality of the rejection of the last Office action is granted, and finality is withdrawn. The Examiner's Answer mailed 12 October 2005 is now designated a non-final office action, in accordance with the Decision on Petition of 30 January 2006. The Reply Brief received 12 December 2005 and the Supplemental Response received 30 March 2006 are being treated as responses to a non-final office action, in accordance with the Decision on Petition.

The Information Disclosure Statement of 30 March 2006 has been received and considered. The second declaration of Dr. Polakis, received 30 March 2006, has also been entered and considered.

Claims 1-123, 127, and 128 are canceled. Claims 124-126 and 129-131 are under examination.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

35 U.S.C. §§ 101 and 112, First Paragraph

Claims 124-126 and 129-131 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility for reasons of record.

Claims 124-126 and 129-131 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a credible, specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention, for reasons of record.

Applicant has submitted arguments in two responses, which will be addressed in turn:

1. Applicant's arguments submitted in the Reply Brief received 12 December 2005 have been fully considered but are not found to be persuasive for the following reasons.

Applicant argues that the rejection uses a legally incorrect standard in requiring that a positive result be shown for most or a larger percentage of the tissue samples studied. Applicant urges that such a requirement is the domain of the FDA, not the USPTO. Applicant argues that the identification of a pharmacologic or diagnostic utility is legally sufficient. Applicant argues hat some tumor markers are useful for identifying rare malignancies, and have great value in tumor diagnosis and prognosis. This has been fully considered but is not found to be persuasive. In the instant case, the claims are directed to polypeptides. The specification asserts that PRO341 polypeptides are elevated in tumor tissues based on gene amplification results; however, the literature evidences that this assumption is a false one. Regarding rare tumor markers, such rare tumor markers are only useful if the type of rare tumor it identifies is known. The specification has not identified anything rare, or anything in common, among the three lung tumor samples in which the PRO341 gene is amplified. PRO341 gene tested

positive in LT16, LT17, and LT21 samples. Table 8 (p. 546) identifies these samples as lung squamous cell carcinoma stage IB, lung squamous cell carcinoma stage IIB, and lung large cell carcinoma stage IIB.

Applicant refers to the Goddard declaration as establishing that an approximately 2-fold amplification of genomic DNA is significant. Applicant argues that the examiner has misrepresented the declaration's reliance on publications. Applicant asserts that Dr. Goddard's own scientific experience and factual findings support the statement in the declaration that a 2-fold amplification is significant. Applicant urges that the examiner must accept the opinion of an expert, referring to the Utility Guidelines. This has been fully considered but is not found to be persuasive. In assessing the weight to be given expert testimony, the examiner may properly consider, among other things, the nature of the fact sought to be established, the strength of any opposing evidence, the interest of the expert in the outcome of the case, and the presence or absence of factual support for the expert's opinion. See Ex parte Simpson, 61 USPQ2d 1009 (BPAI 2001), Cf. Redac Int'l. Ltd. v. Lotus Development Corp., 81 F.3d 1576, 38 USPQ2d 1665 (Fed. Cir. 1996), Paragon Podiatry Lab., Inc. v. KLM Lab., Inc., 948 F.2d 1182, 25 USPQ2d 1561, (Fed. Cir. 1993). In the instant situation, the nature of the fact sought to be established is whether or not a 2.173 to 2.514-fold amplification of the gene encoding PRO341 in three lung tumors is significant. The significance can be questioned since eleven of the fourteen lung tumor samples did not show an amplification of the gene encoding PRO341, and the control used was not a matched non-tumor lung sample but rather was a pooled DNA sample from blood of healthy subjects. The art uses matched

tissue samples (see Pennica et al., Konopka et al.). Hu et al. and Chen et al. speak to the strength of the opposing evidence, as do Pennica et al., Konopka et al., Haynes et al., Gygi et al., Lian et al., and Fessler et al., discussed in the previous Office Action. Also, Greenbaum et al. (2003, Genome Biology 4:117.1-117.8) cautions against assuming that mRNA levels are generally correlative of protein levels. The reference teaches (page 117.3, 2nd column) that primarily because of a limited ability to measure protein abundances, researchers have tried to find correlations between mRNA and the limited protein expression data, in the hope that they could determine protein abundance levels from the more copious and technically easier mRNA experiments. To date, however, there have been only a handful of efforts to find correlations between mRNA and protein expression levels, most notably in human cancers and yeast cells. And, for the most part, they have reported only minimal and/or limited correlations. The reference further teaches (page 117.4, 2nd column) that there are presumably at least three reasons for the poor correlations generally reported in the literature between the level of mRNA and the level of protein, and these may not be mutually exclusive. First, there are many complicated and varied post-transcriptional mechanisms involved in turning mRNA into protein that are not yet sufficiently well defined to be able to compute protein concentrations from mRNA; second, proteins may differ substantially in their *in vivo* half lives; and/or third, there is a significant amount of error and noise in both protein and mRNA experiments that limit our ability to get a clear picture. The reference further notes (page 117.6, page 2nd column) that to be fully able to understand the relationship between mRNA and protein abundances, the dynamic processes involved

in protein synthesis and degradation have to be better understood.

Beginning at p. 8 of the Reply Brief, Applicant addresses the Sen et al. and Hittelman et al. publications relied upon in the rejection set forth in the previous Examiner's Answer. Specifically, Applicant argues that the publications support Applicant's asserted utility in that, even if the gene amplification of PRO341 were due to aneuploidy, the PRO341 gene would still be useful as a cancer diagnostic because aneupliody itself is associated with early detection of cancer. Applicant urges that aneuploidy may be used as a feature to identify cancerous, pre-cancerous, or damaged tissue. Applicant quotes from Sen et al. wherein it is stated that aneuploidy correlates with many cancers or risk or many cancers. Applicant argues that Hittelman et al. report a correlation between genetic instability and epithelial tissues at risk for cancer. Applicant argues that Hittelman et al. establish that the art recognized a shift toward using pre-cancerous indicators for cancer risk assessment and detection of early cancer. This has been fully considered but is not found to be persuasive because the specification asserts that PRO341 is a marker that can be used to diagnose cancer, not pre-cancerous tissue or risk of cancer. Also, it is maintained that gene amplification, or aneuploidy, do not correlate with increased protein levels for reasons of record.

Applicant addresses the Hu et al. and LeBaer publications beginning at p. 10 of the Reply Brief. Applicant indicates that the publications report statistical analysis using literature mining and, as such, do not support lack of utility. This has been fully considered but is not found to be persuasive because Hu et al. and LeBaer provide conclusions based on many research efforts. If anything, their conclusions are even

more probative than those based on a smaller study. Furthermore, the instant specification provides no statistical analysis.

Applicant argues that Gygi et al. is mischaracterized in the Examiner's Answer, and asserts that Gygi et al. report a general trend of correlation between mRNA and protein levels. This has been fully considered but is not found to be persuasive because Gygi et al. state,

> "the correlation between mRNA and protein levels was insufficient to predict protein expression levels from quantitative mRNA data. Indeed, for some genes, while the mRNA levels were of the same value the protein levels varied by more than 20-fold. Conversely, invariant steady-state levels of certain proteins were observed with respective mRNA transcript levels that varied by as much as 30-fold. Our results clearly delineate the technical boundaries of current approaches for quantitative analysis of protein expression and reveal that simple deduction from mRNA transcript analysis is insufficient."

Applicant argues that the Chen et al. publication is not applicable to the instant application because the 2D gels used by Chen et al. exclude key regulatory proteins, an analyze the data in a different manner than the instant application. Applicant urges that Chen et al. show that it is more likely than not that increased mRNA expression correlates well with increased protein expression. This has been fully considered but is not found to be persuasive. Chen et al. compared mRNA and protein expression for a cohort of genes in the same lung adenocarcinomas. Only 17% of 165 protein spots or 21% of the genes had a significant correlation between protein and mRNA expression levels. Chen et al. clearly state that "the use of mRNA expression patterns by themselves, however, is insufficient for understanding the expression of protein

products" (p. 304) and "it is not possible to predict overall protein expression levels based on average mRNA abundance in lung cancer samples" (pp. 311-312).

Applicant refers to a later paper by the Chen et al. authors. However, this paper was not submitted, and is thus not found to be persuasive.

Applicant states that the utility rejection is based upon a misrepresentation of the data presented in the Haynes et al., Gygi et al., and Chen et al. references. This has been fully considered but is not found to be persuasive for the reasons of record.

Applicant argues that the Lian et al. publication is limited to differentiating myeloid cells and does not teach anything regarding a lack of correlation between mRNA levels and protein levels in general. Applicant also finds fault with Lian et al. for using a relatively insensitive assay. This has been fully considered but is not found to be persuasive. Lian et al. show a lack of correlation in mammalian (mouse) cells (see p. 514, top of left column: "The results suggest a poor correlation between mRNA expression and protein abundance, indicating that it may be difficult to extrapolate directly from individual mRNA changes to corresponding ones in protein levels.")

Applicant takes issue with the Fessler et al. publication, stating that Fessler et al. is limited to studying a few proteins/RNAs and using an insensitive assay. This has been fully considered but is not found to be persuasive because Fessler et al. found a "[p]oor concordance between mRNA transcript and protein expression changes" in human cells (p. 31291, abstract).

2. Applicant's additional arguments provided in the supplemental response received 30 March 2006 have been fully considered but are not found to be persuasive for the following reasons.

Applicant submits the Hirsch et al. publication as further evidence that PRO341 has at least one utility as a marker for cancerous or pre-cancerous or damaged tissue. Hirsch et al. is characterized as establishing that lung cancer is a multi-step process involving accruing sequential genetic and cellular changes. This has been fully considered but is not found to be persuasive because the specification asserts that PRO341 is a marker that can be used to diagnose cancer, not pre-cancerous tissue or risk of cancer. Also, it is maintained that gene amplification, or aneuploidy, do not correlate with increased protein levels for reasons of record.

Applicant refers to the second declaration of Dr. Polakis, submitted with the response. Applicant argues that this declaration provides the facts for independent evaluation by the examiner. The second Polakis declaration under 37 CFR 1.132 filed 30 March 2006 is insufficient to overcome the rejection of claims 124-126 and 129-131 based upon 35 U.S.C. §§ 101 and 112, first paragraph, as set forth in the last Office action for the following reasons. The second Polakis declaration sets forth a table that did not appear in the first Polakis declaration. PRO341 does not appear in the table. Also, it is not clear how the clones appearing in the table compare to PRO341. For example, how many of the tumors were lung tumors? How highly amplified were the genes that correlated with increased polypeptide levels?

Applicant submits several references showing a good correlation between mRNA

levels and protein levels for individual genes in cancer. Applicant also provides a publication refuting the findings in Gygi et al. regarding the yeast proteome. These references have been reviewed and appear to support Applicant's position. However, the rejection is maintained over the preponderance of the totality of the evidence. For example, Chen et al. compared mRNA and protein expression for a large number of genes in the same lung adenocarcinomas. Only 17% of 165 protein spots or 21% of the genes had a significant correlation between protein and mRNA expression levels. Chen et al. clearly state that "the use of mRNA expression patterns by themselves, however, is insufficient for understanding the expression of protein products" (p. 304) and "it is not possible to predict overall protein expression levels based on average mRNA abundance in lung cancer samples" (pp. 311-312). Other reviews reach similar conclusions. For example, Greenbaum et al. (2003, Genome Biology 4:117.1-117.8) cautions against assuming that mRNA levels are generally correlative of protein levels. The reference teaches (page 117.3, 2nd column) that primarily because of a limited ability to measure protein abundances, researchers have tried to find correlations between mRNA and the limited protein expression data, in the hope that they could determine protein abundance levels from the more copious and technically easier mRNA experiments. To date, however, there have been only a handful of efforts to find correlations between mRNA and protein expression levels, most notably in human cancers and yeast cells. And, for the most part, they have reported only minimal and/or limited correlations. The reference further teaches (page 117.4, 2nd column) that there are presumably at least three reasons for the poor correlations generally reported in the

literature between the level of mRNA and the level of protein, and these may not be mutually exclusive. First, there are many complicated and varied post-transcriptional mechanisms involved in turning mRNA into protein that are not yet sufficiently well defined to be able to compute protein concentrations from mRNA; second, proteins may differ substantially in their *in vivo* half lives; and/or third, there is a significant amount of error and noise in both protein and mRNA experiments that limit our ability to get a clear picture. The reference further notes (page 117.6, page 2nd column) that to be fully able to understand the relationship between mRNA and protein abundances, the dynamic processes involved in protein synthesis and degradation have to be better understood. It is noted that the Greenbaum et al. reference is cited in response to the new references cited by Applicant in the last response.

Thus, in view of the preponderance of the totality of the evidence, the rejections are maintained.

Conclusion

No claims are allowed.

The Examiner's Answer mailed 12 October 2005 is now designated a non-final office action, in accordance with the Decision on Petition of 30 January 2006. Therefore, **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Elizabeth C. Kemmerer, Ph.D. whose telephone number is (571) 272-0874. The examiner can normally be reached on Monday through Thursday, 7:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, Ph.D. can be reached on (571) 272-0867. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

ECK

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER